ADRENAL TUMORS.

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ALTHOUGH the literature on the subject of adrenal tumors is not an extensive one, it has seemed to me that it would be useful to collate it, and so render it more accessible to students, for it is a scattered one. Such a collation will be based upon the paper of Kelynack, which up to its time was the most useful and comprehensive one in existence. Since the time of its publication many new facts have been added to our knowledge of these tumors, and especially to our knowledge of the malignant growths, which makes it necessary to add to the above-mentioned paper, admirable as it is.

Writers on pathology have not, apparently, been impressed by the remarkable facts discovered in the peculiar tumors in these important organs, for the current text-books—English and German alike—mention few of the common or uncommon features of them. One reason for such a neglect is that the earlier, and the later writers, too, have been interested in the relation between changes in the adrenal glands and Addison's disease, with the result that the case reports are of little or no present value in a large number of cases. There are, however, a few papers which are of much importance in this connection, notably those of Rolleston and Marks, Ramsey, Kelly, and Jores.

In discussing adrenal tumors I shall first deal with the benign tumors and then with the malignant ones.

BENIGN TUMORS. The benign tumors of the adrenals belong in by far the greater number of cases to one class, namely, the adenomata, but the following varieties have also been reported: fibromata, lipomata, neuromata, gliomata, angiomata, and cystomata.

Fibromata have been reported by Saviotti and Mattei, but there is some doubt as to the authenticity of the cases, the general opinion being that they are, in all probability, fibro-adenomata—a class of tumors which is very common, and in which any proportion may exist between fibrous tissue and parenchyma. Fibromata may, however, occur, but are very rare.

Lipomata likewise have been reported—notably one case by Byford—but here, too, the probability is that these cases are tumors simulating lipomata, but in reality being adenomata which have undergone extreme fatty degeneration—a process which is extremely common in the adrenal and especially so in the adenomatous tumors.

Gliomata have been recorded in the literature by Virchow and Marchand. Reports coming from such sources are to be looked on as valuable; but if such tumors do occur they must be rare anomalies, and due to tissue misplacement, for at the present time there is no reason to suspect that the adrenals contain any epidermic elements which could give rise to gliomatous tumors. Indeed, it has been very clearly shown in the past year that the old idea that the medulla of the adrenal was a derivative of nervous tissue is entirely erroneous, and that ganglionic tissue takes no part in the organogenesis.

Neuromata are to be looked upon with much suspicion, and although several cases have been reported by Weichselbaum, Armanni, and Formad, it is a question whether these are not really cases that should be classed as fibromata. If there is an authentic case of neuroma of the adrenal it must be an excessively rare one, and must be derived from one of the ganglia near the gland.

Of the more complex tumors there are three general classes, namely, adenomata, cysts, and angiomata, and in this last class are included two varieties—hæmangiomata and lymphangiomata.

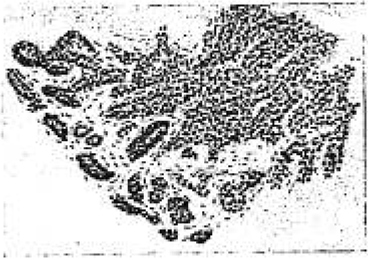
Adenomata in general belong in two categories as regards size and multiplicity in the same organ. The most common are the small multiple adenomata, the large single tumors being far less commonly seen.

The small adenomata appear as yellowish nodules varying in size from a mustard-seed to a small pea. They occupy the medulla and the cortex, and are occasionally found just outside of the cortex, but beneath the capsule. In other words, they may arise in any zone of the organ.

When these are examined microscopically they are seen to be composed of cells which appear like adrenal cells affected by an advanced grade of fatty degeneration.

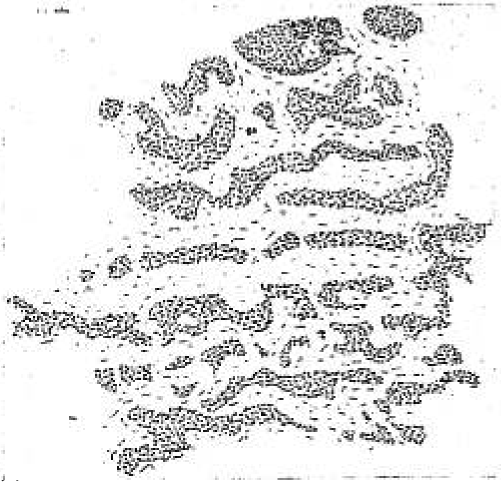
The larger adenomata—which occur singly, but occasionally bilaterally—show in their simpler forms a structure similar to that of the small adenomata, and their cells show the same tendency to fatty change. They usually originate in the cortex of the organ, and while they may form large tumors, they never involve the whole gland, and are usually seen as nodules projecting above the surface of the organ which they occupy. Their structure is more complicated than that of the small adenomata, and the arrangement of their columns of cells may become very intricate, as is the case in any other adenomatous tumor. As they increase in size the cells in the centre of the tumor undergo more or less fatty degeneration, and this process may extend to the supporting tissues, until the centre breaks down to form a cyst with mushy contents, or hemorrhage occurs into the softened tissue, forming a hemorrhagic cyst. By a gradual increase in the hemorrhage a huge cyst may at length be produced, similar to the one reported by Pawlik, which contained 10 litres of bloody material. In such a way, I believe, all the blood cysts of the adrenals arise, for hemorrhage into these adenomata, and indeed into the glands themselves, is not a remarkably uncommon occurrence.

FIG. 1.



Case of cystic fibro-adenoma of adrenal. Zona glomerulosa in the wall of the tumor. Leitz eye piece IV., ocular 3. (Camera lucida.)

FIG. 2.

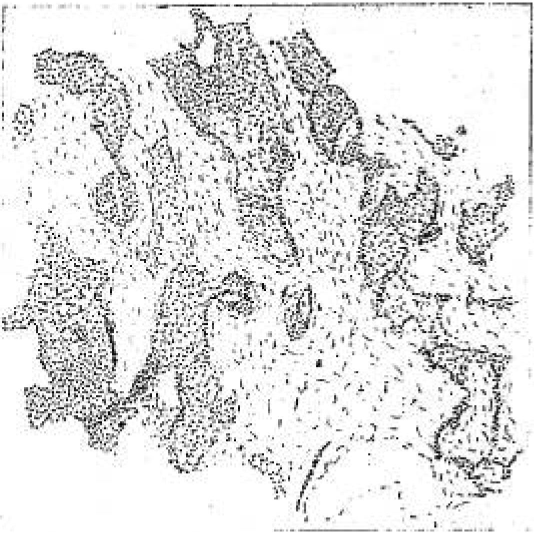


Zona fascicularis in wall of the tumor. Same magnification.

But besides these degenerative changes others may occur, and the resulting tumors have furnished the occasion for the reports of Letulle and Pilliet on "Surrénalites Nodulaires Hyperplastiques" and "Scléroses." In these so-called hyperplastic tumors there has apparently been an increase of the fibrous tissue, so that they come under the head of fibro-adenomata of more or less well-marked types.

The features of such tumors will be most easily remarked, I think, if I describe in some detail a tumor which came into my hands through the kindness of Dr. McCrae, of the Montreal General Hospital. The tumor was accidentally discovered at autopsy, and nothing in the man's history can be shown to be due to the presence of the tumor.

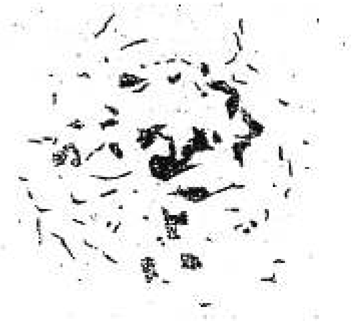
FIG. 3.



Zona reticularis in wall of tumor. Same magnification.

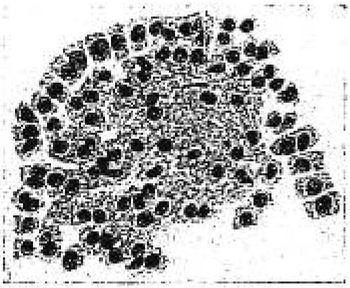
The right adrenal, in which the tumor occurred, was somewhat larger than normal, even if the growth could be neglected, and at one end appeared a rounded protuberance, which was fairly firm and rather elastic. On section the gland itself was apparently normal. The tumor, on section, presented a peculiar appearance. It was partially cystic, its contents being dark-brownish material, rather granular in appearance. The walls of the cyst were yellowish, with dark striations, and firm and tough. At one place there was an area that had the appearance of and cut like cartilage. To the apex of this area, which projected into the cyst, was attached an arborescent mass of tissue, generally quite dark in color, which had the appearance of an intracystic papilloma.

FIG. 4.



Areas of infiltration with lime salts. Leitz E. I., ocular 4.

FIG. 5.



Portion of a column of adrenal cells from zona fascicularis. Leitz E. IV., ocular 6. (Camera lucida.) The stain in all cases has been carbol-thionin.

On section of the wall of the cyst it was at once remarked that inside a compressed layer of fairly normal gland cortex was a fibroid and œdematous layer, composed of masses and columns of gland cells separated by masses of œdematous fibrous tissue, with occasional areas of pigmented material (the remains of old hemorrhage) and a few patches of calcareous deposit. (Figs. 1 to 5.) The area which had appeared like hyaline cartilage proved to be simply a hyaline fibrous tissue with a few nuclei, while the papillary, arborescent mass was the remnant of gland tissue which had not completely degenerated, and which had remained attached to fibrous strands and filled between with hemorrhagic detritus. This cystic fibro-adenoma was the size of a small English walnut.

Besides the hemorrhagic cysts two other varieties have been reported, namely, a serous variety by Ogle and a hydatid cyst by Bennett. This last, however, is a doubtful case, for in the description there are no details that would positively identify it.

Angiomata are rather rare growths, if we consider simply the benign forms, Klebs, Laboulbene, Vogel, and Seltz having reported cases. The case of Payne was a blood vascular tumor, while those mentioned by the other authors were lymphangiomata. They present no unusual features.

MALIGNANT TUMORS. When we come to study the primary malignant tumors of the adrenals we find a rather anomalous group of new-growths. The peculiarities of these tumors depend primarily upon the fact that they have their origin in a tissue that is less stable than epithelium or hypothelium, and which has been differentiated at a comparatively recent time, histogenetically, from the middle germ layer, and which is more closely related to the supporting tissues than are the two covering membranes of the body.

The adrenals are developed from the peritoneum—which in its turn has been a derivative of the middle germ layer—and of that division of mesoderm which we call mesothelium. This mesothelium seems to be the origin of tumors which at one time corresponded morphologically to the class of carcinomata, at another to sarcomata, and at another of a group of tumors which present a likeness to both the above types either in the same or in different nodules. Such tumors various authors have described in too little detail, and one such has furnished me with a text for a paper in which I have discussed at some length the changes which occur and the meaning of these variations. It will, therefore, suffice to mention here that the feature of greatest interest is the tendency for adrenal tumors of carcinomatoid appearance to form nodules, which may be purely sarcomatous or sarcocarcinomatoid, as the case may be. Rolleston and Marks and others emphasize this point.

As types of malignant tumors originating in the adrenals the following have been mentioned: carcinomata, sarcomata, endotheliomata, and peritheliomata.

In looking over the literature I have been unable to satisfy myself that the latter two varieties exist, although I have specimens of an aberrant adrenal tumor of the kidney that was distinctly a perithelioma; so these may exist also in the adrenal itself. If they do occur, and if they have the characteristics of the aberrant tumor that I have seen, they are tumors which show the ordinary characteristics of the malignant vascular tumors.

The other malignant tumors of the adrenals fall into two classes as they are described—*i. e.*, sarcomata and carcinomata. This classification rests, of course, on purely morphological grounds—a basis which is absolutely inadequate, White to the contrary notwithstanding—for many reasons, which I have discussed and which are sufficiently obvious. In my paper I described the tumor that I was studying as mesothelioma.

These adrenal mesotheliomata—or mesolepidomata, as Adami calls them—occur as large or small tumors, circumscribed or infiltrating, and originate in one of the zones of the cortex of the adrenal gland. When circumscribed they metastasize chiefly by the bloodvessels, but also by the lymph vessels in a certain number of cases. When they are infiltrating they may involve any of the neighboring organs, chiefly the liver and kidney, and are especially prone to invade the inferior vena cava. When small they may give rise to no symptoms that aid diagnosis, but they may give rise to many and serious symptoms by their metastases. The larger tumors produce various symptoms of tumor—such as a palpable, movable, or fixed mass in the renal region —and especially to symptoms of venous obstruction, due to pressure on, or thrombosis of, the vena cava. Metastasis, as a rule, occurs by the bloodvessels, and is most common in the liver and lungs. In twenty-two cases which I have collected from the literature which can be called carcinomata by the postulates of Rolleston and Marks there were metastases, as follows:

Liver	13 times.
Lungs	11 "
Lymph glands	7 "
Brain	3 "
Kidney	2 "
Peritoneum	3 "
Appendix	1 time.
Stomach	1 "
Mesentery	1 "
Pericardium	1 time.
Endocardium	1 "
Uterus	1 "
Ovary	2 times.
Spleen	1 time.
Bones	2 times.
Diaphragm	1 time.
Bladder	1 "

These tumors occur at all ages. The youngest was nine months (Cohn) and the oldest seventy-three years (Ritchie and Bruce). In Ramsey's list of thirty-seven carcinomata[1] twenty-two were in men, and in my list of twenty-two, eleven were in men. I shall append a table of the cases of the carcinomatoid tumors judged by the postulates of Rolleston and Marks.

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[1] It will be seen from these figures that Ramsey has given a longer list of primary carcinomata than I. This is because I do not feel that many of the cases quoted by him are primary, as judged by the rules of Rolleston and Marks, which I think are very useful and very logical, considering that "judgment is difficult."

The microscopic appearances of the malignant adrenal tumors vary. I have seen none that show purely sarcomatous appearances, but, judging by some of the descriptions in the literature, they do occur. Indeed, they are the more common variety. They conform in appearance to other sarcomata, and are spindle-celled or round-celled in type. The carcinomatoid tumors have an alveolar appearance corresponding in a certain extent with the arrangement of the normal gland. In some instances they have a peculiar perivascular arrangement, which I think is uncommon.

The primary tumor may correspond to the carcinomata even in the arrangement of the reticulum, but there is a tendency for the reticulum to become intercellular even when in the larger part of the tumor it surrounds groups of cells. In the case which I described the reticulum in the primary tumor separated groups of cells, while in the metastases, in lymph glands, and brain it was intercellular. In the lungs the arrangement took on characters of the so-called carcinoma-sarcomatodes. The origin of these tumors has been shown to be, at least in some cases, in the parenchyma of the organs, and is not due to connective-tissue changes or to proliferation of the cells of the bloodvessels.

Finally, the cells of malignant adrenal tumors, like those of other malignant growths, are larger as a rule, the nuclei are larger comparatively, the protoplasm less in amount, and the nuclear substance more abundant than normal. Mitotic figures, regular and atypical, are common.

The most noticeable feature in these tumors is their well-marked tendency to variation in type, due to the remarkable inclination of the cells to metaplastic changes.

In the accompanying tabulation of the primary carcinomatoid adrenal tumors there will be found a brief epitome of the characters and clinical observations abstracted from the case reports. In the tabulation I cannot include the cases of Stybr and Nuno Porto, because I have not been able to read the first or obtain the second paper, and because I have been unable to find any adequate abstract of either case. It has, however, been asserted by several authorities that the first was a primary melanotic carcinoma, and that the second was also a primary growth.

SECONDARY MALIGNANT GROWTHS. Secondary tumors are not uncommon, and occur in persons past middle life in the great majority of cases. In looking over the autopsy records of the Royal Victoria Hospital I was able to find mention of secondary sarcoma in one case in fifteen; of secondary carcinoma in seven cases in forty-eight.

The case of sarcoma occurred in a case of multiple sarcoma, and nodules were found in both adrenals. The cases of carcinomata occurred as follows: cancer of the stomach with metastases in the left adrenal, three times; in the right adrenal, twice; cancer of the pancreas, in both adrenals, once; cancer of the bile-duct, in both adrenals, once; in the left, once; cancer of the intestines, in the right adrenal, once.

NOTE.—Since I have had the proofs of the preceding remarks, I have come across three interesting papers that had escaped my notice, in spite of my care in searching the literature.

One of these papers is that of Morris (*Brit. Med. Journ.*, 1899, vol. ii. 1336), which discusses three cases of adrenal growths, all of which the author considers to be sarcomata, although, as he says, the resemblance to carcinoma is a very marked feature in some cases of the growths. The first case has been recorded in the *Reports of the Middlesex Hospital* (1888, p. 230) as a "Sarcoma of the Adrenal." It occurred in a man, aged fifty-one years, and weighed 61½ ounces. The left adrenal only was involved. His second case was in a man, aged forty-three years, and in this instance the tumor was on the right side. No autopsy was obtained, and there is some doubt as to whether the growth was certainly primary in the adrenal.

The third case was that of a woman, aged forty-three years. In this case the growth was a cystic sarcoma, and after operation the patient died, with recurrences.

The second paper is that of Orr (*Edin. Med. Journ.*, 1900, vol. l.), who reports a case of sarcoma in a child, aged seven weeks. Both adrenals were affected. The liver was involved by the growth. Dr. Leith gives a good pathological discussion of the findings, and decides that the case is one of small round-celled sarcoma, although it could be distinguished only with some difficulty from carcinoma. This is the youngest case on record.

Three of these cases then deserve to be classed with the so-called "primary sarcomata," the other is possibly primary.

The third paper is that of Schnittenhelm (*Wien. klin. Rundschau*, 1901), and in this paper a case of medullary cancer of both adrenals in a man, aged fifty-five years, is described. This case may be one of primary carcinoma. The remarkable features of this case are the clinical symptoms, which Schnittenhelm ascribes to an auto-intoxication. There was no pigmentation.

TABLE OF PRIMARY CARCINOMATOID ADRENAL TUMORS.

No.	Source.	Publication.	Sex and age.	Gland.	Nature.	Secondary growths.	Pigmentation.	Remarks.
1	Rolleston and Marks,	Amer. Journ. Med. Sci., n.s., vol. cxvi. p. 116.	Male, 50	Left.	Round-cell carcinoma.	Liver, peritoneum.	None.	Ascites; œdema of feet. Diagnosis: abdominal aneurism.
2	Ibid.,	Ibid.	Male, 40	Right.	Round-cell carcinoma.	Right and left lungs, liver, aortic glands.	None.	Pneumonia.
3	Ibid.,	Ibid.	Female, 52	Right.	"Malignant adenoma."	Liver.	None.	Anæmia; leucocytosis; emaciation; enlarged liver and spleen; kidney invaded; pleural effusion; ascites; œdema of legs.
4	Ogle,	Trans. Path. Soc., London.	Female, 3	Left.	"Malignant adenoma."	Liver.	"Gypsy color."	Constant vomiting; weight increased; pubic hair, moustache; colon depressed.
5	Ritchie, Bruce,	Edinburgh Med. Journ.	Male, 78	Both.	Carcinoma.	Lungs.	None.	Vomiting.
6	Weinburg, Turquet,	Bull. Anat. Soc., Paris.	Female, 36	Both.	Carcinoma.	Both lungs, cerebellum, appendix.	…………	Dilated stomach; diarrhœa; lumbar pain; vomiting; severe headache.
7	Fenwick,	See Rolleston and Marks.	Male, 62	Right.	Carcinoma.	Liver, mesentery, stomach; pancreas invaded by continuity.	None.	Pulsation (not expansile); left adrenal enlarged; vena porta and vena cava inferior thrombosis; six ounces of blood clot in tumor; blood-stained fluid in peritoneal cavity.
8	Brooks,	Redcliffe Infirmary.	Female, 49	Left.	Carcinoma.	Liver, lungs, right adrenal, bronchial glands.	None.	Irregular temperature; emaciation; pain down left leg.
9	Ibid.,	Roy. Col. Surg. Museum.	Female, 32	Right.	Carcinoma.	Liver and aortic lymph glands.	…………	Growth into vena cava inferior; hypertrichosis.
10	Carrière Délearde,	Arch. de Méd. Expér.	Male, 54	Both.	"Epitheliome atypique."	Liver, lungs.	None.	Palpable tumor; œdema of legs; cachexia; diarrhœa; pleural effusion; ascites.
11	Pawlik,	Arch. f. klin. Chirurgie.	Female, 50	Both.	Melanotic carcinoma.	Right kidney, brain, lungs, pleuræ, epicardium, endocardium, peritoneum, liver, and uterus.	…………,	Extension of right kidney; loss of appetite; vomiting; increased urine; right facial paralysis; right pupil dilated; almost complete amnesia; right hemiplegia; urine and feces passed involuntarily.

12	Bruchanow,	Zeits. f. Heilkunde.	Female, 14 mos.	Right.	Medullary carcinoma.	Lymph glands, right ovary.	....	Thrombosis inferior vena cava; œdema of feet; extension to liver.
13	....	....	Male, 63	Right.	Carcinomatous degeneration of a struma.	Liver and right lung; lymph glands.	....	Extension to liver; œdema of feet; asthenia.
14	....	....	Female, 66	Right.	Cancer.	Lymph glands; spleen.	....	Growth in kidney a collateral development in accessory gland.
15	Orth,	Arbeiten Göttingen.	Female, 4½	Right.	Carcinoma.	Liver and lungs.	....	Abnormally developed genitalia.
16	....	....	Male, 49	Left.	Carcinoma.	Liver.	....	Death from marasmus.
17	Marchand,	Virchow's Festschrift.	Female, 20	Right.	Carcinoma.	Left ovary, liver.	....	Irregular menstruation; œdema of legs.
18	Collinet,	Bull. Anat. Soc., Paris.	Male, 53	Right.	Epithelioma.	Diaphragm, renocæcal ligament.	None.	Œdema of legs; loss of appetite; growth extended to liver and kidney; cells in portal vein.
19	Stoukoventoff,	Gaz. Méd. de Paris.	Female, 50	Both	Carcinoma.	Liver and lungs.	None.	Fever; pain over liver; liver enlarged; sanguineous expectoration; œdema of legs; albuminuria; dyspnœa; cyanosis.
20	Possolt,	Wien. klin. Woch.	Male, 46	Left.	Carcinoma.	Left lung, kidney, lumbar vertebræ.	Present.	Had pulmonary tuberculosis and Addison's disease; symptoms of these.
21	Kelly,	Ziegler's Beiträge.	Male, 68	Left.	Carcinoma.	Bladder and lungs.	....	Metastasis by inferior vena cava.
22	Woolley,	Journ. Exp. Medicine.	Male, 42	Both.	Mesothelioma.	Right lung, brain, lymph glands.	None.	Fainting attacks; weakness; dyspnœa; incontinence of urine and feces; symptoms of meningitis; frontal headache; vomiting; optic neuritis.

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ON ADRENALIN GLYCOSURIA AND CERTAIN RELATIONS BETWEEN THE ADRENAL GLANDS AND CARBOHYDRATE METABOLISM.

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THE adrenal gland was for the first time brought into relation with glycosuria by F. Blum,[1] of Frankfort, who in September, 1901, published observations showing that extracts of the adrenal glands of sheep are capable of inducing a slight or moderate grade of glycosuria when injected subcutaneously into dogs and rabbits. The results of Blum were confirmed in Europe, and led in this country to experiments with Takamine's adrenalin chloride and Abel's adrenalin which have extended our information as to the glycosuria following the administration of preparations made from the adrenals. Herter and Richards[2]

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[1] Ueber Nebennierendiabetes, Deutsches Archiv für klin. Medicin, Bd. lxxi.

[2] Medical News, February 1, 1902.